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SCIENTIFIC INVESTIGATIONS

Relationship of Metabolic Syndrome and Obstructive Sleep Apnea

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Study Objectives: Obstructive sleep apnea (OSA) and metabolic syndrome represent significant risk factors for the development of cardiovascular disease. The purpose of this study was to see how frequently metabolic syndrome occurred in patients with OSA and whether the presence of metabolic syndrome was correlated with age, sex, or severity of OSA.

Methods: We examined the records of 250 consecutive patients referred to our Sleep Disorders Center to have polysomnography for the evaluation of OSA and extracted clinical data from the patients' medical records. We compared the proportion of patients with OSA and metabolic syndrome, hypertension, diabetes, or dyslipidemia to the group without OSA. We also did subgroup analysis by age and sex.

Results: A total of 228 patients were included in the study. Of 146 patients with OSA, 88 (60%) had metabolic syndrome, whereas 33 of 82 patients (40%) without significant OSA had metabolic syndrome (p = .004). The proportion with hypertension was significantly higher in the OSA group (77% vs 51%; p = .001). The proportion of patients with hyperglycemia and dyslipidemia was not significantly different between the 2 groups. In men older than age 50 years, there was a significantly higher than expected proportion of OSA patients with metabolic syndrome and in the proportion with hypertension but not with a diagnosis of diabetes or dyslipidemia. In women (both older and younger than age 50), and in men younger than age 50, there was not an independent relationship between metabolic syndrome and OSA.

Conclusions: Patients with OSA have a high prevalence of metabolic syndrome. The prevalence of metabolic syndrome and hypertension was significantly greater in the OSA group. No significant differences were noted between the 2 groups in the proportion of patients with diabetes and dyslipidemia.

Keywords: Diabetes; hypertension; insulin resistance; metabolic syndrome; obesity; obstructive sleep apnea

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Obstructive sleep apnea (OSA) syndrome has been associated with an increased incidence of hypertension, stroke, and cardiovascular disease.[1] Metabolic syndrome, also known as insulin resistance syndrome, is recognized as a constellation of obesity, glucose intolerance, dyslipidemia, and hypertension. Over the past several decades, there has been a substantial increase in the prevalence of metabolic syndrome, coinciding with the increased prevalence of obesity. The significance of metabolic syndrome is that the combination of these risk factors predisposes patients to the early development of cardiovascular disease.[2]

Although there are variations in the definition of metabolic syndrome in different studies, virtually all include the presence of some combination of obesity, hyperglycemia, dyslipidemia (hypertriglyceridemia or low high-density lipoprotein cholesterol) and hypertension in an individual patient. The prevalence of metabolic syndrome is approximately 22.8% of US men and 22.6% of US women.[3] Obesity has been demonstrated to be the main precursor of the metabolic syndrome,[4] and it is also a clinically significant factor in the development of OSA, although it is but 1 of many risk factors.[5] Because OSA and metabolic syndrome are associated with obesity and an increased risk of cardiovascular disease, we hypothesized that there would likely be an association between OSA and metabolic syndrome. We therefore sought to identify the prevalence of metabolic syndrome in a group of patients referred to a sleep center for evaluation of OSA.

METHODS

A retrospective review was conducted for 250 consecutive patients referred to the Sleep Disorders Center of the Mayo Clinic Hospital, Phoenix, Arizona, for evaluation of OSA between January and April 2004. Patients were referred for polysomnography on the basis of clinical indications identified by the patients and their physician in the course of their usual clinical care. All patients underwent overnight polysomnography at a hospital-based sleep laboratory. All studies included 2 channels of electroencephalogram, electrooculogram, submental electromyogram, nasal-oral airflow measurement by pressure transducer, chest and abdominal wall motion by respiratory inductive plethysmography, oximetry, single-lead electrocardiography, and electromyogram of both anterior tibialis muscles. Sleep staging was scored by rules of Rechstaffen and Kales.[6] Apneas were defined by an 80% or greater reduction in the airflow signal with persistent respiratory effort lasting 10 seconds

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Table 1—Patient Characteristics

Characteristic	Results[a]		
Total group, (N = 228)			
Age, y	63.2 ± 13.9 (15-89)		
BMI	32.2 ± 7.7 (16.7-60.1)		
Female sex, % (no./total)	41 (93/228)		
OSA vs non-OSA	**AHI ≥ 5 (n = 174)**	**AHI < 5 (n = 54)**	**p Value**
Age, y	63.4 ± 12.77	56.1 ± 15.2	<0.001
BMI	32.2 ± 7.6	32.4 ± 8.0	0.88
Female sex, %	34	63	<0.001
AHI	29.7 ± 23.8	2.2 ± 1.5	<0.001
OSA vs non-OSA	**AHI ≥ 10 (n = 146)**	**AHI < 10 (n = 82)**	
Age, y	65.7 ± 12.43	58.6 ± 15.3	<0.001
BMI	32.5	32.0	0.64
Female sex, %	29	62	<0.001
AHI	33.5 ± 22.6	3.9 ± 2.9	<0.001

[a]Values are mean ± SD (range) unless indicated otherwise. BMI refers to body mass index; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index.

or longer. Hypopneas were defined as a 30% or greater reduction in the airflow signal with persistent respiratory effort lasting at least 10 seconds associated with a desaturation of 4% or greater. Additional measurements included body weight on a single scale in the Sleep Disorders Center, resting/seated blood pressure, and abdominal and hip circumference.

All patients were seen in consultation by a member of the Sleep Disorders Center medical staff prior to polysomnography, and medical records were available for all patients in the Mayo Clinic electronic medical record database. From the patient's medical record, we abstracted clinical information that included the cholesterol profile, current treatment with lipid-lowering medications, presence or absence of hypertension, current treatment with antihypertensive drugs, and fasting glucose or current treatment with insulin or oral hypoglycemic agents. The laboratory studies were done as part of the usual clinical workup. All data had to have been collected within 3 months of the date of the polysomnography to be included in the analysis. The timing of the laboratory studies was not part of the study protocol because these data were abstracted from medical records. The diagnosis of metabolic syndrome was based on the following criteria: (1) abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women), (2) elevated triglyceride level (≥ 150 mg/dL) or a low level of high-density lipoprotein cholesterol (≤ 40 mg/dL for men and ≤ 50 mg/dL for women) in patients not currently using lipid-lowering medications, (3) a diagnosis of dyslipidemia in patients currently using a lipid-lowering medication, 94) elevated blood pressure (systolic ≥ 130 mm/Hg or diastolic ≥ 85 mm/Hg) or current use of antihypertensive drugs, and (5) fasting plasma glucose level (≥ 110 mg/dL) or current use of insulin or oral diabetic medications. Patients who met 3 or more criteria were identified as having metabolic syndrome. The study was approved by the Mayo Clinic Institutional Review Board.

Statistical Analysis

We compared the proportions of our study sample with metabolic syndrome stratified by the presence of OSA. We used a definition of an apnea-hypopnea index (AHI) of both ≥ 5 and ≥ 10 for classifying patients as having OSA to determine whether there were any differences between these 2 frequently used definitions of OSA. We also compared the presence or absence of hyperglycemia, dyslipidemia, or hypertension between patients diagnosed with or without OSA. We applied χ^2 testing to assess statistical significance for the comparisons. A p value of .05 or less was considered to be statistically significant. The data were also analyzed using a trend test to assess the association between the severity of OSA and the components of metabolic syndrome.

Univariate subset analysis was completed using population subsets to assess the association with OSA. Subset-analysis components included patient age, sex, and metabolic syndrome. We compared the proportion of patients with metabolic syndrome in patients with OSA who were younger than age 50 years with those older than age 50, and we compared male and female patients. The age-50 cutoff was chosen to attempt to see if there were differences in premenopausal women versus postmenopausal women. The statistical testing in the subset evaluation used χ^2 and the Fisher exact test for contingency table analysis.

RESULTS

There were 250 individual consecutive patients seen in consultation and studied in our Sleep Disorders Center during the study period. Of these patients, 228 had sufficient data available in their medical record for analysis. For the 228 patients from whom data were analyzed, the mean age was 63.2 years, the mean body mass index (BMI) was 32.2, and 41% were women (Table 1). There were 146 patients with an AHI ≥ 10 and 82 patients with an AHI < 10. The mean age (65.7 vs 58.6 years; p < .001) was older in the OSA group, but the mean BMI was not significantly different between the 2 groups (32.5 vs 32.0; p = .64). The OSA group had a significantly greater percentage of men, compared with the non-OSA group (62% vs 29%; p<.001). For the 22 patients with insufficient data for analysis, the mean age was 62 years (range, 30-80 years) and the mean BMI was 28.6 (range, 22-40.7); 6 were women (24%), and 13 had an AHI > 5 (60%). Compared with those of the study group, the mean age, BMI, and proportion of patients with an AHI > 5 were not significantly different; the proportion of women was slightly lower.

Of the entire group of 228 patients, 121 patients were found to have metabolic syndrome, and 107 patients were classified as not having metabolic syndrome (Table 2). Sixty percent of patients

Table 2—Prevalence of Metabolic Syndrome and Components in 228 Consecutive Patients

Diagnosis	Finding[a]		p Value
	AHI ≥ 5 (n = 174)	AHI < 5 (n = 54)	
Metabolic syndrome	98 (56)	23 (43)	0.08
Hyperglycemia	53 (30)	15 (28)	0.64
Dyslipidemia	97 (56)	28 (52)	0.69
Hypertension	125 (72)	29 (54)	0.01
	AHI ≥10 (n = 146)	AHI <10 (n = 82)	
Metabolic syndrome	88 (60)	33 (40)	0.004
Hyperglycemia	47 (32)	21 (26)	0.30
Dyslipidemia	82 (56)	43 (52)	0.62
Hypertension	112 (77)	42 (51)	<0.001

[a]Values are number (percentage) unless indicated otherwise. AHI refers to apnea-hypopnea index.

with OSA (AHI > 10) met the definition for metabolic syndrome, whereas 40% of those without OSA had metabolic syndrome (p = .004). The data were also analyzed using a definition of OSA with an AHI ≥ 5. The prevalence of metabolic syndrome was similar to that for OSA using a definition of an AHI of ≥ 10. Fifty-six percent of patients with OSA had metabolic syndrome, whereas 43% of patients without OSA had metabolic syndrome; this difference, however, did not reach statistical significance (p = .08).

Hypertension was significantly more common in patients with OSA than in patients without OSA (Table 2). In patients with OSA, using a definition of AHI ≥ 10, the proportion with hypertension was 77%, compared with 51% in the group with an AHI < 10. Using the criterion of AHI ≥ 5, 72% of OSA patients had hypertension, compared with 54% whose AHI was < 5. The difference between the proportions with hypertension was significant in both groups. However, the proportion of patients with either hyperglycemia or dyslipidemia was not significantly different between the 2 groups, irrespective of the cutoff definition of OSA.

The prevalence of metabolic syndrome was correlated with the severity of OSA (Table 3). For the group with an AHI < 5, 43% had metabolic syndrome; in contrast, in the group with an AHI ≥ 30, 70% had metabolic syndrome (p = .01). The proportion with hypertension was directly correlated with the severity of OSA (p < .001). In comparison, the proportion of patients with diabetes or dyslipidemia was not correlated with the severity of OSA.

Men and women were analyzed separately for prevalence of metabolic syndrome and its components (Table 4). Men were slightly older, had a lower BMI, a higher AHI, and more dyslipidemia. Hypertension, hyperglycemia, and metabolic syndrome were also more common in men but were not statistically significant. A subset analysis by the sex of patients demonstrated that male patients with OSA were more likely to have metabolic syndrome than were male patients without OSA. The mean BMI was not statistically different between these groups. In women, the presence of OSA was not associated with a statistically significant increase in the proportion with metabolic syndrome (Table 4). In Table 5, the subset analysis looked at the association of metabolic syndrome and OSA in both men and women stratified by age above and below 50. Male patients older than age 50 with OSA with AHI cutoffs of 10 and 15 were more likely to have metabolic syndrome than were male patients older than age 50 without OSA. In contrast, in male patients younger than age 50, there was no significant difference in the proportion with metabolic syndrome between the group with and without OSA. In women, no significant association was observed between OSA and metabolic syndrome in either group: younger than age 50 or older than age 50.

The proportion of subjects with metabolic syndrome and its components were analyzed separately for both men and women stratified by the presence of OSA using AHI cutoffs of 5 and 10 (Table 6). In women, a diagnosis of OSA was not associated with the presence of metabolic syndrome, hyperglycemia, dyslipidemia, or hypertension. In men, a diagnosis of OSA, using a cutoff AHI of 10, was associated with the presence of metabolic syndrome and a diagnosis of hypertension (p < .01). However, an independent association with hyperglycemia or dyslipidemia was not observed. When men with OSA (defined as AHI ≥ 5 and ≥ 10) were compared with women with OSA, there were no significant differences in proportion with metabolic syndrome, hyperglycemia, dyslipidemia, or hypertension (Table 6).

DISCUSSION

Several key findings were noted in the study. Metabolic syndrome is common in patients with OSA because obesity is a shared risk factor. Analysis of metabolic syndrome component variables shows that hypertension is the primary variable associated with a diagnosis of OSA. Metabolic syndrome is associated with OSA when an AHI cutoff of 10 or higher is used. Finally, metabolic syndrome is associated with increasing severity of AHI. However, in our study population, there was not an independent association of hyperglycemia or dyslipidemia with OSA. Our data would support a hypothesis that, while OSA is associated with hypertension and obesity, there does not seem to be an independent association with a clinical diagnosis of diabetes or dyslipidemia. Obesity is likely the main predisposing factor for diabetes and dyslipidemia seen in these patients.

Table 3—Prevalence of Metabolic Syndrome and Its Components as a Function of the Severity of Obstructive Sleep Apnea in 228 Consecutive Patients[a]

Diagnosis	AHI < 5 (n = 54)	AHI 5-14 (n = 57)	AHI 15-29 (n = 57)	AHI ≥30 (n = 60)	p value
Metabolic syndrome	23 (43)	28 (49)	28 (49)	42 (70)	0.01
Hyperglycemia	15 (28)	14 (25)	18 (32)	21 (35)	0.24
Hypertension	29 (54)	33 (58)	39 (68)	53 (88)	<0.001
Dyslipidemia	28 (52)	33 (58)	28 (49)	36 (60)	0.59

[a]Values are expressed number (percentage) unless indicated otherwise. AHI refers to apnea-hypopnea syndrome.

Table 4—Characteristics of Men and Women[a]

Characteristic	Men (n = 135)	Women (n = 93)	p Value
Age, y	64.7 ± 12.8 (25-85)	60.9 ± 14.6 (15-75)	0.05
BMI	31.3 ± 13.2 (16.3-67)	33.6 ± 8.8 (16-56)	0.03
AHI	29.9 ± 26.6 (0-118)	13.5 ± 14.3 (0-75)	<0.001
Metabolic syndrome	77 (57)	43 (46)	0.18
Hyperglycemia	43 (32)	28 (30)	0.77
Dyslipidemia	84 (62)	46 (49)	0.01
Hypertension	99 (73)	56 (60)	0.06

[a]Values are expressed as mean ± SD (range) or number (percentage). BMI refers to body mass index; AHI, apnea-hypopnea index.

Table 5—Proportion of Patients With Metabolic Syndrome by Age[a]

OSA by AHI[b]	Women (n = 93) Age, y		Men (n = 135) Age, y	
	> 50	< 50	> 50	< 50
> 5	28/50 (56)	3/9 (33)	59/99 (60)	8/16 (50)
> 10	20/34 (59)	3/8 (38)	58/92 (63)‡	7/12 (58)
> 15	15/27 (56)	1/6 (17)	49/75 (65)‡	5/9 (56)

[a]Values are expressed as number/total (percentage).
[b]Comparison was made between patients with and without obstructive sleep apnea (OSA). The Fisher exact test was used for χ^2 analysis. Significance was defined as $p < .05$.
‡$p < .05$.

Cardiovascular disease is the leading of cause of death in the United States. Multiple risk factors identified as contributors to the development of coronary heart disease include age, cigarette smoking, obesity, high blood pressure, diabetes, and dyslipidemia. Several of these risk factors (eg, obesity, hypertension, dyslipidemia, and hyperglycemia) cluster in certain persons and have been called syndrome X, insulin resistance syndrome, or metabolic syndrome. Other features associated with metabolic syndrome are microalbuminuria, hypercoagulability, increased inflammatory mediators, and endothelial dysfunction.[7,8] The presence of metabolic syndrome has been reported to be associated with an increased incidence of all cardiovascular disease.[2,9-11] Hu et al,[12] summarizing 11 prospective European cohort studies comprising more than 11,000 subjects, reported that the overall hazard ratio for cardiovascular mortality in persons with, compared to without, metabolic syndrome was 2.26 in men and 2.78 in women after adjustment for age, cholesterol levels, and smoking.

Cardiovascular disease, especially hypertension, has been associated with OSA.[8] The Sleep Heart Health Study demonstrated convincingly that OSA is an independent risk factor for hypertension and all cardiovascular disease.[1] OSA has also been associated with hypertension on the basis of animal studies[13] and other large epidemiologic studies.[14-16] OSA has also been associated with an increase in various inflammatory markers associated with the development of atherosclerosis, including C-reactive protein and interleukin-6.[17] Additionally, OSA has been associated with endothelial dysfunction, a known precursor to the development of atherosclerosis.[18,19]

Recent investigations have also shown that OSA is associated with insulin resistance and that glucose metabolism is altered in patients with OSA, compared with those without OSA.[20-22] Sleep-disordered breathing has been noted to be independently associated with glucose intolerance, insulin resistance, and an increased incidence of type 2 diabetes.[23,24] However, in another study, Resnik et al,[25] using data from the Sleep Heart Health study, compared diabetic patients with nondiabetic patients and found no statistically significant difference in OSA between the 2 groups, although there was a difference in the proportion of diabetic patients with periodic breathing. These investigators concluded that the association of diabetes observed in patients with OSA could be explained by factors common to both disorders, most likely obesity and other confounding variables. Coughlin

Table 6—Proportion of Patients With Metabolic Syndrome and Its Various Components in Women and Men[a,b]

Characteristic	Women (n = 93)				Men (n = 135)			
	AHI <5 (*n* = 34)	AHI ≥5 (n = 59)	AHI <10 (n = 51)	AHI ≥10 (n = 42)	AHI <5 (n = 20)	AHI ≥5 (n = 115)	AHI <10 (n = 31)	AHI ≥10 (n = 104)
Age, y	55.7 ± 15.6 (15-89)	63.9 ± 13.3 (31-90)	59.8 ± 15.8 (15-75)	62.3 ± 13.2 (31-83)	56.5 ± 14.7 (29-51)	66.1 ± 12.5 (25-85)	56.6 ± 14.3 (29-80)	67.1 ± 12.5 (25-85)
BMI	34.5 ± 8.75 (20.4-72.6)	33.2 ± 8.9 (16.3-63.6)	33.2 ± 8.2 (18.3-72.6)	34.4 ± 9.6 (16.3-63.6)	29 ± 5.1 (24.5-48)	31.7 ± 6.8 (16-67)	30 ± 5.1 (24.5-47.9)	31.7 ± 7.0 (16.3-67)
AHI	2.1 ± 1.5 (0-4.8)	20 ± 14.3‡ (5.1-75.4)	3.7 ± 2.76 (0-9.4)	25.4 ± 13.8‡ (10.6-75.4)	2.3 ± 1.63 (0-4.9)	34.7 ± 26‡ (5.1-118)	4.15 ± 0.5 (0-9.7)	37.5 ± 25.7‡ (10.3-118)
Metabolic syndrome, no. (%)	13 (38)	31 (53)	21 (41)	23 (55)	10 (50)	67 (58)	12 (39)	65 (63)‡
Hyperglycemia, no. (%)	10 (29)	16 (27)	14 (27)	12 (29)	4 (20)	38 (33)	7 (23)	35 (34)
Dyslipidemia, no. (%)	13 (38)	33 (56)	24 (47)	22 (52)	15 (75)	65 (57)	19 (61)	64 (62)
Hypertension, no. (%)	18 (53)	38 (64)	27 (53)	29 (69)	11 (55)	87 (76)	14 (45)	83 (80)‡

[a]Values are number ± SD (range) unless indicated otherwise. BMI refers to body mass index.
[b]Analysis of the proportion of each group with metabolic syndrome and its components was stratified by sex and then by severity of obstructive sleep apnea on the basis of the apnea-hypopnea index (AHI. Continuous data (age, body mass index, and apnea-hypopnea index) were analyzed by the 2-tailed *t* test assuming unequal variance. Categorical data were analyzed by χ^2 analysis using the Fisher exact test. Significance between groups was defined as $p < .05$.
‡$p < .05$.

et al[26] found that, compared with controls, patients with OSA have higher blood pressure, higher fasting insulin, increased insulin resistance, lower levels of high-density lipoprotein, and an increased incidence of metabolic syndrome. In this latter study, the group with OSA had a higher BMI than the group without OSA, which raises the possibility that obesity rather than OSA is a primary determinant of metabolic syndrome. Ip et al[20] observed in patients with OSA that obesity was the major determinant in insulin resistance, although sleep-disordered breathing also had a smaller but independent effect on insulin resistance. Of interest, Tauman et al[27] recently found in a study of children with OSA that obesity, not sleep-disordered breathing, was the major determinant in glucose intolerance and altered lipidemia. Sharma et al,[28] in a case control study of patients with OSA and nonapneic obese subjects, found that obesity, but not OSA, was independently associated with lipid abnormalities, measures of insulin resistance, serum leptin, and serum adiponectin levels.

We found in our study group that patients with OSA had a significantly higher prevalence of the metabolic syndrome, as compared with those without OSA. The main variable that seemed to account for this difference was the presence of hypertension. The prevalence of neither diabetes mellitus nor dyslipidemia was significantly different between the 2 groups. There was also a positive association between the severity of OSA and the presence of metabolic syndrome, which suggests that the more severe the sleep apnea, the more likely the patient was to have metabolic syndrome. However, hypertension was the only component of metabolic syndrome associated with the severity of OSA. We also analyzed the subset of individuals younger than age 50 compared with those older than 50 to see if the relationship with metabolic syndrome differed by age. We found that OSA was associated primarily with hypertension and metabolic syndrome in male patients older than age 50. In our study group, there was not an association of OSA with metabolic syndrome in either male or female patients younger than age 50.

Our study has several limitations. The data were collected retrospectively rather than prospectively. However, we reviewed the records of consecutive patients in the sleep laboratory, so there was no selection of patients. The purpose of the study was to collect preliminary data for a prospective study on metabolic syndrome and OSA. We did not always have access to the lipid profiles of patients before they were started on lipid-lowering agents, and we therefore included individual patients using any lipid-lowering medication, including statins, as meeting the criteria for dyslipidemia. Also, the OSA group consisted of a significantly greater number of male patients than there were in the non-OSA group, which is another potential confounding factor. However, an important strength of the data is that the mean BMI was similar between the 2 groups, making it less likely that any differences could be explained solely on the basis of obesity.

Our study demonstrates that a large proportion of patients with OSA have metabolic syndrome. Both conditions represent risk factors for development of atherosclerosis and cardiovascular disease. The presence of hypertension seems to be the factor most closely associated with the presence of metabolic syndrome in a patient with OSA. The results of standard biochemical testing and physical examination make identification of metabolic syndrome readily apparent. The data support the concept that the medical evaluation of patients who meet the criteria for a diagnosis of metabolic syndrome should also take into consideration the diagnosis of OSA. Further research should focus on the interaction of OSA, obesity, hypertension, measurements of insulin resistance, and endothelial dysfunction as risk factors for cardiovascular disease.

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